Case No. F7526(V)

REMARKS

Reconsideration of the application, as amended, is respectfully requested.

Claim 1 has been amended to recite an antibody or fragment capable of binding to "a" human dietary lipase. Claim 1 no longer recites explicitly "one or more" so it would appear that the Office's objections to that language are moot (Office Action, paragraphs 4-5.) Claim 2 has been amended to correct informalities. Claim 4 has been amended to improve the form for prosecution in the U.S.. Likewise, claims 3, 9 and 10 have been amended to improve the form for prosecution in the U.S. in accordance with the Examiner's suggestions.

It is known that VHHs can be used in various products and that VHHs are more stable than traditional antibodies. However, the undersigned has been informed that one of ordinary skill knows that effector functions as present on traditional antibodies such as IgGs are important for the antibody to function and inactivate or clear certain agents, substances, proteins, or even cells or viruses from the body. VHHs lack certain effector functions, but the present specification (example 5) indicates that they are able to reduce lipase activity *in vitro* and *in vivo*. This is surprising for the reasons set out below.

Antibodies may inhibit lipases by (1) binding to the active site, (2) by targeting it for removal/destruction, (3) by binding to the lipase molecule in such a way that it can bind to the oil water interphase required for activation (steric hindrance; intact antibodies are much bigger than the lipase enzyme, VHH are smaller than the lipase enzyme).

Although it is known that VHHs are functional with respect to antigen recognition and binding, VHHs are not bivalent like normal IgG antibodies (or multivalent like IgMs). The undersigned has been informed that they therefore will not or to a lesser extent cause agglutination and precipitation of antigen (lipases). Classical antibodies may also inhibit by targeting antigen (lipases) for destruction and thereby effectively remove the lipase; (this free (active) equilibrium). Removal is brought about by the effector functions on the antibody, signaling the immune system to recruit macrophages and stimulate further immune responses against the antigen, normally via activation of the complement pathway.

Applicants wish to point out that VHHs lack several of the effector functions, in that they do not have a CH1 domain on the heavy chain and a lack of light chain sequences altogether.

Hence, Applicants submit that it is surprising that the VHHs disclosed in the current invention are still capable of effectively inhibiting lipase activity *in vitro* and even *in vivo* in the gastrointestinal tract of a subject.

The Office asserts that the skilled person would have a reasonable expectation of success trying to replace classical antibodies raised against lipases with VHHs. WO 99/46300 teaches "that VHHs are comparable to mouse MAbs in specificity and affinity." Although this in itself may be true, Applicants submit that a high affinity for an antigen per se does not necessarily lead to inhibition of enzyme activity, either by the binding itself to the catalytic site or by destruction or cleaning of the enzyme. This is even more so given the inhibition of enzyme activity in the gastrointestinal tract, which has a

rather hostile environment for an antibody to be functional. This is also alluded to in the cited prior art document of Aoubala.

Furthermore, although the prior art does show lipase specific antibodies, Applicants contend that the Office points to no teaching actually disclosing lipase inhibitory activity in the gastrointestinal tract, as disclosed in the current invention. The current invention teaches that instead of intact classical Ig's, heavy chain immunoglobulins may be used and, more importantly, that instead of using intact, bivalent antibodies comprising all antibody functions, heavy chain mono-valent fragments (which are at least 10 times smaller) can be effective *in vitro* and *in vivo*.

In view of the foregoing, it is respectfully requested that the application, as amended, be allowed.

Respectfully submitted,

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